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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/689,992	10/13/2000	Craig C. Mello	07917-105001 / UMMC 00-04	1020

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/689,992	MELLO ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 November 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *03 November 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *14,17-22 and 35-42*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

TS 11/16/04

JEFFREY FREDMAN
PRIMARY EXAMINER
11/18/04

Continuation of 5. does NOT place the application in condition for allowance because:

Applicants' arguments regarding the objection to specification were found persuasive, therefore the objection is withdrawn. However, Fig. 10B should be modified to reflect changes made to SEQ ID NO: 5.

Applicants' arguments with regards to the written description, enablement and art rejections were considered but they were not found to be persuasive.

Regarding the rejection of claims 14, 17, 19-22 and 35 under 35 U.S.C. 112, first paragraph, written description, Applicants argue tha the genus of RDE-1 and RDE-4 polypeptides and homologs "are extensively described in the specification". As pointed out in the final office action mailed on May 3, 2004, the total number of amino acid sequence homologs, as determined by Applicants on the basis of amino acid sequence searches against databases, was four for RDE-1 and two for RDE-4, as can be seen from Figures 4 and 11. Applicants did not show that these proteins can function in the same way as RDE-1 or RDE-4 in terms of promoting RNA interference. Applicants did not define the term "homolog", therefore, in its broadest definition, it includes both structural homologs, defined on the basi of amino acid sequence searches or domain homologies, and functional homologs, i.e., proteins from any organism which are functionally related to RDE-1 and RDE-4. Therefore, out of hundreds of thousands of possible proteins, Applicants described, at the very best, eight proteins. The rejection is maintained.

Regarding the rejection of claims 14, 17-22 and 35 under 35 U.S.C. 112, first paragraph, scope of enablement, Applicants argue that examiner's unpredictability arguments are directed mainly to the PKR response in mammalian system, and that means to counteracting the PKR response were known to skilled artisans at the time of the filing of the instant application. However, the unpredictability of the RNAi response in mammalian systems was noted in the very recent references of record of Heaphy et al. (published 2001), Paddison et al. (published in 2002), Caplan (published in 2002) and Scherr (published in 2003). Applicants' application was filed on October 13, 2000 If the only issue was PKR response and the ways of counteracting it were known, none of these articles should have been published. Th fact that three years after Applicants' filing date the proces of RNAi silencing is still considered unpredictable points to the fact that a lot o factors are involved, all of which would need to be determined, which, taking into account the number of possible proteins involved, as claimed, would take more than routine experimentation to perform.

Applicants further assert that since the RDE-1 and RDE-4 belong to conserved gene families and other members of these families have been described by Applicants, the experimentation would not be undue. First, Applicants described six other proteins with amino acid sequences homologous to RDE-1 and RDE-4, without providing any evidence that their function is similar to that of RDE-1 or RDE-4 Applicants' claim language encompasses proteins which are functional homologs of RDE-1 or RDE-4 and which have not been discovere yet. Further, Applicants claim not only proteins which closely related to RDE-1 or RDE-4 by amino acid homology, but any protein which is a "member of the RNAi pathway", which may mean any protein which in any way interacts with RDE-1 or RDE-4 or their structural or functional homologs, which means potentially hundreds of proteins. Applicants' claims also read on using proteins of one organism to silence genes in another organism, the process to which no guidance was provided. Therefore, evaluation of all of these proteins in term of their role of gene silencing in the organism from which they are derived and in other organisms would definitely require undue experimentation. The rejection is maintained.

Regarding the rejection of claims 14, 35 and 36 under 35 U.S.C. 102(b) as anticipated by Fire et al. and the rejection of claim 20 under 35 U.S.C. 103(a) over Fire et al. and Wheeler et al., Applicants argue that examiner errs by interpreting the claim language as introduction of dsRNA into the cell, whereas the claim requires introduction of an RNAi agent into the cell, and the specification describes RNAi agent as dsRNA which has been treated with RNAi pathway component. However, the method of claim 14 does not require that the step of RNAi agent preparation and introduction into the cell be separate steps in the order of first RNAi preparation and then RNAi introduction into the cell. Therefore, since, as pointed by Applicants, "Another method of preparing an RNAi agent is to activate the RNAi pathway in a target cell (i.e., a cell in which it is desirable to activate the RNAi pathway such as a tumor cell) by transgenesis of an RDE-1 coding sequence and an RDE-4 coding sequence into the target cell." (Page 28, lines 28-31), the claim limitations are anticipated by Fire et al., since the RNAi pathway components are present in the cell into which the dsRNA is introduced. The rejections are maintained.